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Scientific Letter

4 Weeks Versus 5 Weeks of Hypofractionated High-dose Radiation Therapy as Primary Therapy for Prostate Cancer: Interim Safety Analysis of a Randomized Phase 3 Trial

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Summary

In the present randomized phase III trial, we evaluated the incidence in toxicity of 2 different hypofractionated radiation therapy regimens. This preplanned safety interim analysis has confirmed that both regimens are safe and that the study can be continued.

Purpose: Hypofractionated radiation therapy (HFRT) for localized prostate cancer is safe and effective. The question that remains is which hypofractionation schedule to implement. We compared 2 different HFRT regimens in the present study.

Methods and Materials: From June 2013 to July 2016, 160 patients with prostate cancer were randomly assigned (1:1), within this single-center phase III trial, to 56 Gy (16 fractions of 3.5 Gy; arm A) or 67 Gy (25 fractions of 2.68 Gy; arm B). Randomization was performed using computer-generated permuted blocks, stratified by previous transurethral resection of the prostate and the presence of a dominant intraprostatic lesion. Treatment allocation was not masked, and the clinicians were not blinded. The primary endpoint was acute gastrointestinal (GI) toxicity, assessed using the Common Terminology Criteria for Adverse Events, version 4.0, and Radiation Therapy Oncology Group toxicity scale. An interim analysis of acute toxicity was planned at 160 patients to prove the safety of both treatment regimens. If $\geq$22 of 72 patients had grade $\geq$2 GI toxicity, the study arm would be rejected. The study is registered at ClinicalTrials.gov (NCT01921803).

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Results: In arm A, 20 patients (26%) and 1 patient (1%) developed acute grade 2 and grade 3 GI toxicity. In arm B, 16 patients (20%) reported acute grade 2 GI toxicity. In arm A, 42 (55%) and 5 (6%) patients developed acute grade 2 and grade 3 urinary toxicity. In arm B, 40 (49%) and 7 (9%) patients reported acute grade 2 and grade 3 urinary toxicity. Toxicity peaked during radiation therapy and resolved in the months after radiation therapy.

Conclusions: With acute grade ≥2 GI toxicity reported in 21 of 77 patients in arm A and 16 of 82 patients in arm B, both treatment arms can be considered safe.

Introduction

Recently, 4 randomized trials comparing conventional-dose radiation therapy (RT) with hypofractionated RT (HFRT) demonstrated the noninferiority of HFRT for biochemical and clinical relapse-free survival for patients with low- and intermediate-risk prostate cancer (1-4). Although increased toxicity was reported, the risk of developing toxicity remained acceptable with HFRT (1-3). Based on the results of these trials, HFRT can be considered a standard of care for localized prostate cancer.

With the proven effectiveness of different HFRT schedules, the side effects will determine which HFRT schedule to apply. Therefore, we initiated a randomized phase III study to compare 56 Gy delivered in 4 weeks (arm A) and 67 Gy delivered in 5 weeks (arm B). An interim safety analysis was planned to decide whether the study could be continued. We report the results of the interim safety analysis, which focused on the incidence of acute gastrointestinal (GI) and urinary toxicity, and the time evolution of acute GI and urinary toxicity.

Methods and Materials

The ethics committee of Ghent University Hospital approved the present single-center, multistage, randomized phase III study, which has been registered at ClinicalTrials.gov (ClinicalTrials.gov identifier NCT01921803). A total of 160 patients were prospectively enrolled from June 2013 to July 2016.

Patients with histologically confirmed stage T1-T4N0M0 prostate cancer and World Health Organization performance status of 0 to 2 were eligible. After written informed consent, the patients were randomized 1:1. Randomization was performed by computer-generated permuted blocks with stratification by previous transurethral resection of the prostate and the presence of a dominant intraprostatic lesion.

Individuals assigned to arm A received 56 Gy in 16 fractions of 3.5 Gy delivered 4 times weekly. Individuals in arm B received 67 Gy in 25 fractions of 2.68 Gy daily, 5 times weekly. Both regimens were calculated to deliver a normalized isoeffective dose of 80 Gy (α/β ratio 1.5 Gy) on the prostate. Before RT, all the patients underwent an abdominopelvic planning computed tomography scan in the treatment position. Magnetic resonance imaging of the prostate (consisting of T1- and T2-weighted imaging and diffusion-weighted imaging) was performed unless contraindicated.

The clinical target volume (CTV) contained the prostate and the whole seminal vesicles. The latter were excluded from the CTV at a normalized isoeffective dose of 50 Gy when the risk of involvement was <15% (5). The planning target volume was created using an isotropic 5-mm margin around the CTV. If a dominant intraprostatic lesion was found on magnetic resonance imaging, it was delineated separately and used for the simultaneous integrated boost. The dose objectives for the targets and organs at risk are presented in Table E1 (available online at www.redjournal.org). Planning was performed using intensity modulated RT with a 7-beam setup. Patient positioning was controlled using daily cone beam computed tomography.

The primary outcome was GI toxicity occurring during or within 3 months after HFRT. Toxicity was scored using Common Terminology Criteria for Adverse Events, version 4.0 (6) and the Radiation Therapy Oncology Group (RTOG) toxicity scale (7). The secondary endpoints were acute urinary toxicity, late toxicity (including erectile dysfunction), quality of life, biochemical control, disease-free survival, distant metastasis-free survival, prostate cancer-specific survival, and overall survival.

The study was designed to include 2 stages. For the first stage, the sample size was calculated to rule out an upper limit of 40% of acute Common Terminology Criteria for Adverse Events version 4.0/RTOG grade ≥2 GI complications, with an expected rate of 25% (derived from our previous study of HFRT) (8), based on a 1-stage Fleming-A'Hern design. A power of 83% (α level of 0.038 one-sided) would be obtained at 72 patients per group. If ≥22 of the 72 patients developed acute grade ≥2 GI complications, the study arm would be rejected. To allow for a withdrawal rate of 10%, 160 patients were included in the first stage. The sample size for the second stage was calculated analogously to rule out an upper limit of 35% of patients with grade ≥2 bowel complications, with an expected rate of 25%. The inclusion of 155 patients per group would result in a power of 86% (α level of 0.049 one-sided). If ≥45 of 155 developed acute grade ≥2 GI complications, the study arm would be rejected. The sample size for the first and second stage combined was set at 346, with a 10% allowance for withdrawal.

The statistical analysis system (SAS), version 9.4 (SAS Institute), was used. Differences in toxicity before and after HFRT were tested using the Friedman test and Wilcoxon signed rank test (cutoff value for significance, $P = .017$).

Results

From June 26, 2013 and June 18, 2016, 160 patients were enrolled in the first stage (Fig. E1; available online at www.redjournal.org). All but 2 patients received the protocol-assigned RT dose and schedule. After allocation to arm A, 1 patient refused participation and received 76 Gy in 38 fractions. Another patient assigned to arm A received the 25-fraction regimen by mistake. Finally, 77 patients received 16 fractions and 82 patients received 25 fractions. In arm B, 2 patients died of non−cancer-related cardiac cause at 1 month after HFRT, resulting in 77 and 80 patients eligible for evaluation per treatment protocol of acute toxicity at 3 months after HFRT in arms A and B, respectively. The acute toxicity data are presented per treatment protocol arm. The patient and tumor characteristics before randomization were equally distributed (Table E2; available online at www.redjournal.org).

GI toxicity

Of the 77 patients evaluated in arm A, 35 (45%), 20 (26%), and 1 (1%) developed acute grade 1, 2, and 3 GI toxicity, respectively. Of the 82 patients evaluated in arm B, 46 (56%) and 16 (20%) reported acute grade 1 and 2 GI toxicity, respectively. No acute grade 3 GI toxicity was observed in arm B. Severe acute upper GI toxicity was not

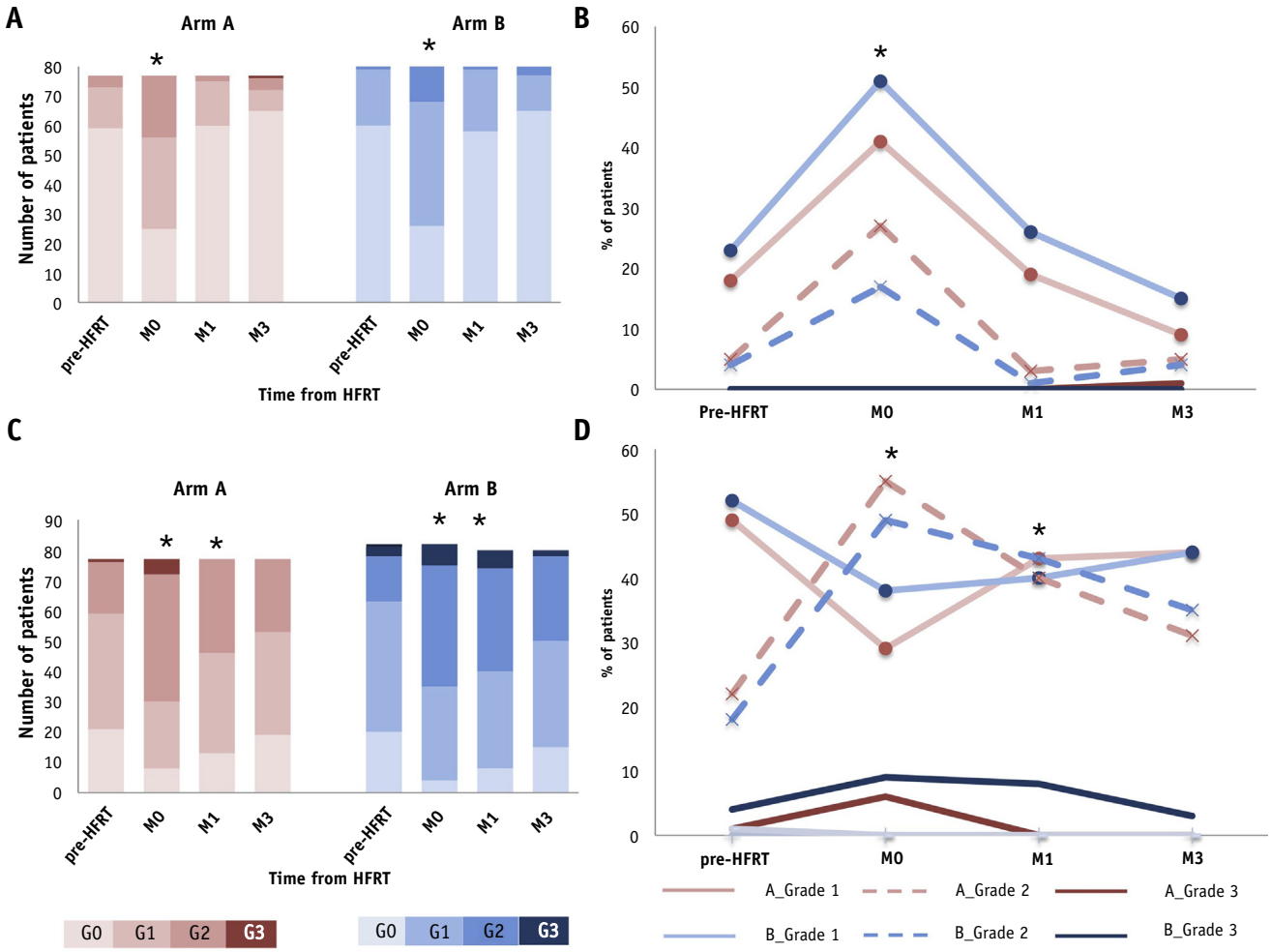

Fig. 1. Evolution in time of gastrointestinal (GI) toxicity and urinary toxicity per treatment group. (A) Distribution of grade 0 to 3 GI toxicity per treatment arm. Data for arm A included toxicity for 79 patients at all time points and for arm B, 82 patients before and 80 patients at 1 and 3 months after hypofractionated radiation therapy (HFRT) (2 patients died at 1 month of follow-up). (B) Graph showing evolution over time of grade 1 to 3 GI toxicity. (C) Distribution of grade 0 to 3 urinary toxicity per treatment arm. Data for arm A included toxicity for 79 patients at all time points and for arm B, 82 patients before and 80 patients at 1 and 3 months after HFRT (2 patients died at 1 month of follow-up). (D) Graph showing evolution over time of grade 1 to 3 urinary toxicity. *Statistically significant difference in toxicity scores before and after HFRT. *Abbreviation:* M = month.

reported. For both arms, diarrhea was the most frequently observed acute grade 2 toxicity.

In both arms, GI toxicity was greatest during and at the end of HFRT and was significantly increased compared with the status before HFRT (arm A, $P < .0001$; arm B, $P < .0001$). However, recovery to the status before HFRT was observed for most patients over time (Fig. 1A and 1B).

Urinary toxicity

In arm A, 22 (29%), 42 (55%), and 5 (6%) patients developed acute grade 1, 2, and 3 urinary toxicity, respectively. In arm B, 31 (38%), 40 (49%), and 7 (9%) patients reported acute grade 1, 2, and 3 urinary toxicity, respectively. Retention, nocturia, and pollakisuria were the most frequently observed acute grade 2 urinary toxicities, reported by >30% of patients in both arms. Similar to rectal toxicity, urinary toxicity was greatest during and at the end of HFRT (arm A, $P < .0001$; arm B, $P < .0001$; Fig. 1C and 1D).

Discussion

Our study results have confirmed that the incidence of acute grade 3 GI toxicity is extremely low. The incidence of acute grade 2 GI toxicity in arm B was in line with the toxicity reported in the Conventional or Hypofractionated High Dose Intensity Modulated Radiotherapy in Prostate Cancer trial and compared favorably with the incidence of GI toxicity of the HYPRO (hypofractionated irradiation for prostate cancer) trial (Table 1) (1, 9). The greater incidence of acute grade ≥2 GI toxicity in arm A might add to the evidence that multiple fractions of >3.4 Gy/d is associated with a greater risk of developing acute GI toxicity (9).

Our results regarding acute grade 3 urinary toxicity were also in line with the results reported in the CHHiP, PROFIT (prostate fractionated irradiation trial), and RTOG trials, and the incidence remained far below the 20% incidence observed in the HYPRO study (1-3, 9). In contrast, our incidence of acute grade 2 urinary toxicity was substantially greater (Table 1) (1-3, 9). This can be explained by the ~20% of our patients who had grade 2 urinary symptoms before HFRT. Baseline toxicity is a significant predictor for both GI and urinary toxicity (10).

Nevertheless, HFRT-induced toxicity appears to be temporary. For both treatment arms, we found a clear peak incidence in acute bowel and urinary toxicity during RT that resolved in the months after RT. A similar pattern has been described in the CHHiP trial (11).

We acknowledge that, owing to the small sample size, small changes in toxicity could have been missed. Another limitation of the present study was that it was a single-center study. Reporting on acute toxicity is important, because it is a significant predictive factor for the development of late toxicity (8). Longer follow-up is required to evaluate whether our applied HFRT regimens are safe and effective in the long term.

Table 1 Overview of acute toxicity reported in different randomized hypofractionation trials compared with our acute toxicity data

Variable	Dearnaley et al (1)		Lee et al (3)	Catton et al (2)	Aluwini et al (8)	Present study	
						Arm A	Arm B
Schedule	20 × 3 Gy		28 × 2.5 Gy	20 × 3 Gy	19 × 3.4 Gy	16 × 3.5 Gy	25 × 2.68 Gy
Scoring system	LENT/SOMA supplemented with RMH scoring system and RTOG		CTCAE, version 3.0	RTOG	RTOG, EORTC	CTCAE, version 4.0	
Time point	4 wk	18 wk	Maximum toxicity ≤90 d after EBRT	Worst grade of toxicity during first 14 wk	Maximum toxicity within 3 months after EBRT	Maximum toxicity ≤3 mo after EBRT	
GI toxicity (%)							
Grade 1	68*	22*	32	43	32	43	56
Grade 2	27*	3	10	16	36	29	20
Grade 3	0	0	1	1	6	1	0
Grade 4	0	0	1	0	0	0	0
Urinary toxicity (%)							
Grade 1	80*	25*	35	45	30	29	38
Grade 2	32*	5	24	27	40	55	49
Grade 3	4*	0	3	4	20	6	9
Grade 4	0	0	0	0	1	0	0

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; EBRT = external beam radiation therapy; EORTC = European Organization for Research and Treatment of Cancer; GI = gastrointestinal; LENT/SOMA = late effects on normal tissue/subjective, objective, management, analytic; RMH = Royal Marsden Hospital; RTOG = Radiation Therapy Oncology Group.

* Data derived from Figure 1 and represent grade ≥1, ≥2, and ≥3 toxicity.

Conclusions

The present interim analysis of acute toxicity after 2 HFRT schedules for prostate cancer has demonstrated the safety of both regimens. Nevertheless, the incidence of GI and urinary toxicity was not negligible and warrants further follow-up.

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